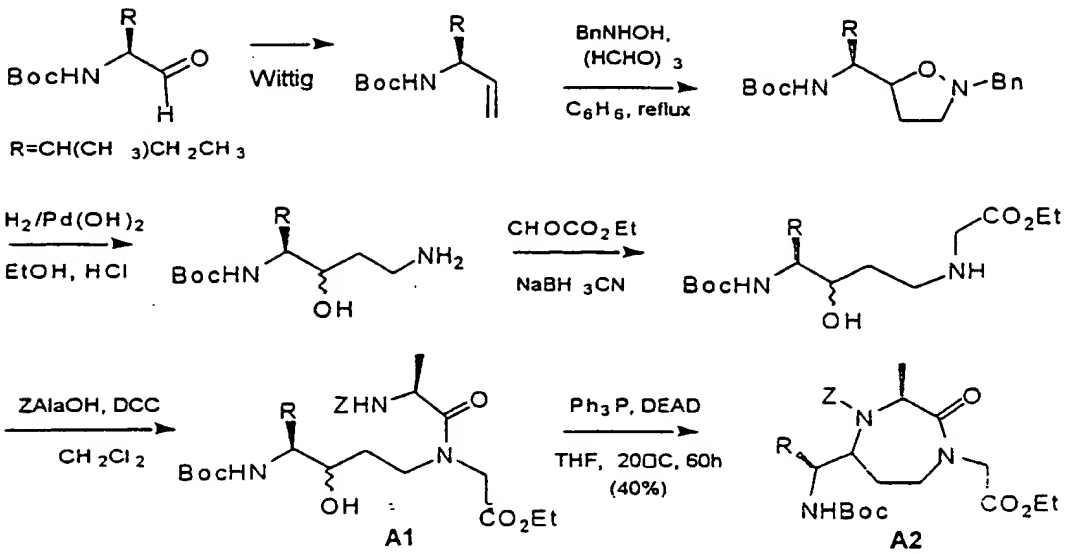
APPENDIX

Previous reports of the □-turn mimetic system **I(i)**

A theoretical study of the suitability of various heterocyclic systems as □-turn mimetics has been published (Alkorta *et al.*, 1996). The study included the 1,3,5-substituted-1,4-diaza-2-oxocycloheptane system (the basis of the □-turn mimetics described herein). No synthesis was described or referenced in the paper for this mimetic system, in contrast to other known mimetic systems where the synthesis was referenced.

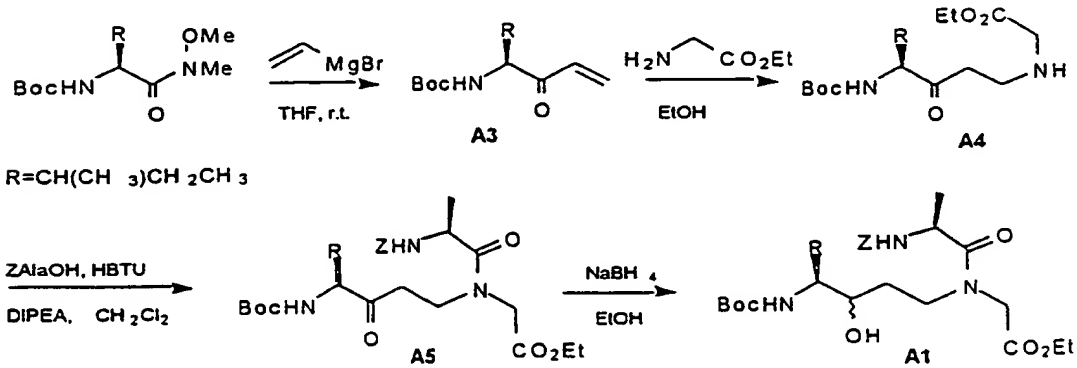
Although a search of the Chemical Abstracts registry file on the substructure of the □-turn system gave only the above modelling study, we are aware of a reported synthesis of the □-turn mimetic system by a different synthetic approach. The alternative approach was described in a poster presented at the 23rd European Peptide Symposium (1994), and repeated at the end of a review published in the Bulletin of the Chemical Society of Belgium (Guilbourdenche *et al.*, 1994) and again the following year (Ma *et al.*, 1995). Our research and other literature results do not support this alternative method, the reports are in error and do not represent a reduction to practice. We have repeated the cyclisation reaction described by Ma *et al.*, 1995 and confirmed by NMR analysis and chemical transformation that the actual product is a structural isomer, not the □-turn mimetic claimed. The synthesis and analyses and other material in support of the assertion that the method of Ma et al. does not represent a reduction to practice are presented below.



Scheme A1 Synthesis proposed by Ma *et al.*, 1995 for a 1,4-diazepine □-turn mimetic.

The key step in the proposed synthesis of Ma *et al.*, 1995 is the cyclisation of **A1** to the protected target **A2** using the Mitsunobu reagents. We repeated the synthesis of the cyclisation precursor by our own methods as described below.

The alcohol **A1** was more conveniently prepared by the conjugate addition method described earlier than as illustrated in Scheme A1 (4 steps vs. 6 steps). The procedure used is summarised in Scheme A2.



Scheme A2

Thus the Weinreb amide of Boc isoleucine was reacted with vinyl Grignard in THF to give the □-□ unsaturated ketone **A3** by the following procedure: Boc-isoleucine-N-methoxy-N-methylamide (2.25 g, 8.2 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0°C under nitrogen. To the stirred solution was added vinyl magnesium bromide in THF (20 mL of a ~1M solution) over 5 min. The reaction was very slow at 0°C (negligible progress over 1 h), but much faster at room temperature (~70% product after 20 min). After stirring at room temperature for 90 min the reaction was poured into crushed ice/1M HCl and extracted with ether. The organic layer was washed with 0.5M HCl, water, aq.$NaHCO_3$ then brine and then dried over $MgSO_4$. The crude product was formed in good yield and purity and was used directly for the next reaction. TLC 25%EA/light pet. Rf=0.64. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 6.50, 1H, dd, J = 10, 17 Hz; 6.37, 1H, dd, J = 1, 17 Hz; 5.85; 1H, d, J = 10 Hz; 5.23, 1H, bd, J = 7 Hz; 4.58, 1H, dd, J = 4, 8 Hz; 1.88, 1H, m; 1.45, 9H, s; 1.32, 1H, m; 1.10, 1H, m; 0.98, 3H, d, J = 7 Hz; 0.90, 3H, d, J = 7 Hz. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 199.0; 155.7; 134.0; 129.6; 79.60; 61.71; 37.50; 28.28 (Boc); 24.09; 16.04; 11.61.

Reaction of **A3** with glycine ethyl ester in ethanol to give **A4** by the following procedure: Glycine ethyl ester hydrochloride (1.0 g, 7.1 mmol) was reacted with **A3** (1.1 g, ~4.7 mmol) and DIEA (450 mg, 3.5 mmol) in ethanol (20 mL) at room temperature overnight. The reaction was diluted with ether (100 mL) and extracted in turn with aq. $NaHCO_3$ and water (x3). Petroleum ether was added (100 mL) and the solution extracted with 0.5M HCl:MeOH 4:1 (x3) (discard the organic layer). The acid washings were immediately neutralised with solid $NaHCO_3$ and then extracted with ethyl acetate and the ethyl acetate layer washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* left 800 mg (~50%) of crude product of sufficient purity for use in the next reaction. TLC EtOAc Rf=0.52. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 209.0; 171.7; 155.8; 79.57; 63.95; 60.76; 50.67; 43.69; 40.82;

36.74; 28.19 (Boc); 24.05; 16.01; 14.08; 11.51. Mass Spectrum (ISMS) m/z 345 (MH^+), calculated for $C_{17}H_{32}N_2O_5$: 344.

The amino ketone **A4** (690 mg, 2 mmol) was then coupled with Z-alanine to give **A5** using standard solution phase coupling procedure with HBTU reagent and DIEA in CH_2Cl_2/THF. The crude product was purified by flash chromatography eluting with 30% EtOAc in light petroleum for a yield of 94% (1.03 g). TLC EtOAc:light pet. 1:2 Rf=0.25. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.34, 5H, m; 5.68, 1H, bm; 5.18-5.02, 3H, m's; 4.72, 0.5H, m; 4.48-4.07, 5H, m's; 3.88-3.54, 2.5H, m's; 2.75-2.05, 2H, m's; 1.89, 1H bs; 1.44, 1.43: 9H, 2s, Boc; 1.38, 1.5H, d, J = 6.9 Hz (alaH□, one rotamer); 1.34-1.28, 5.5H, m's; 1.07, 1H, m; 1.00-0.82, 6H, m's. **^{13}C NMR** (75 MHz, $CDCl_3$), signals due to the equivalent carbon in different rotamers are grouped in parentheses where possible: □ (209.0, 207.9); (173.39, 173.25); (169.15, 168.84); 155.75, 155.67, 155.56, 155.33: carbamate signals; 136.20; 128.31; 127.91; 127.80; (79.72, 79.57); 66.60; (64.01, 63.85); (61.61, 61.09); (50.96, 48.65); (46.63, 46.57); (43.75, 43.23); (40.02, 39.07); (36.56, 36.29); 28.14 (Boc); (24.09, 24.03); 18.74; 15.92; 13.85; (11.44, 11.38). Mass Spectrum (ISMS) m/z 550 (MH^+), calculated for $C_{28}H_{43}N_3O_8$: 549

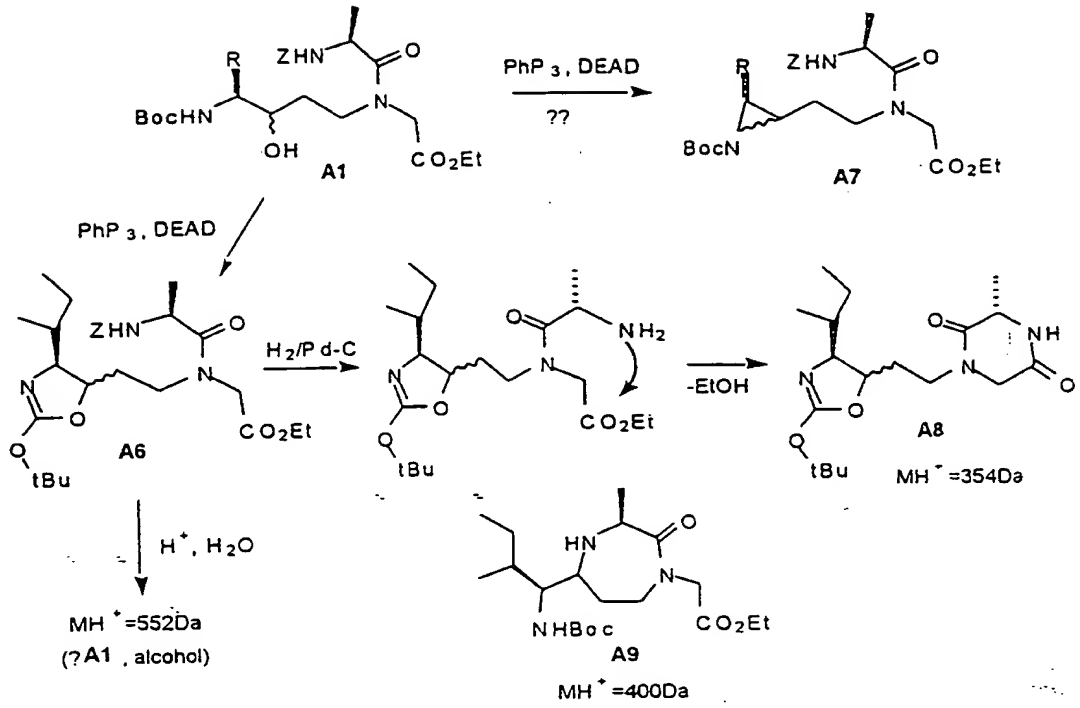
The ketone **A5** (430 mg, 0.78 mmol) was dissolved in ethanol (5 mL) and $NaBH_4$ (15 mg, 0.40 mmol) added to the stirred solution at room temperature, and stirring continued for 1 h. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and washed with 1M HCl, water, aq. $NaHCO_3$, brine and then dried over $MgSO_4$. The residue after solvent evaporation was purified by flash chromatography eluting with ethyl acetate:light petroleum ~1:1 (some separation of diastereomers occurred) for an approximately quantitative yield of the alcohol **A1**. TLC EtOAc:light pet. 1:1 Rf=0.28. **^{1}H NMR** (300 MHz, $CDCl_3$), late eluting fractions, rotamers/diastereomers >2:1: □ 7.39-7.29, 5H, m; 5.80, 1H, d, J=9 Hz; 5.15, 1H, d, J=12 Hz; 5.11-5.49, ~1H, m; 4.96, ~1H, d, J=12 Hz; 4.67-4.42, ~1H, m's; 4.19, ~2H, bq, J=7.2 Hz; 4.03-3.88, ~2H, bm; 3.88-3.40, ~4H, m's; 3.30-3.09, 1H, m; 1.96-1.66,

~2H, m; 1.55, ~1H, m; 1.42, 9H, s, (Boc); 1.331.33, d, J=7 Hz; 1.28, t, J=7.2 Hz; 1.15, d (minor isomer), J=6.8 Hz; 1.37-1.05 ~8H; 1.0-0.82, ~6H, m's. **^{13}C NMR** (75 MHz, $CDCl_3$), major peak only shown unless otherwise indicated: □ 174.0; 169.0; 156.4; 156.3; 135.9; 128.4; 128.1; (128.0, minor isomer); 127.9; 78.92; 66.96; (66.56, minor isomer); 66.11; 61.26; 59.49; 47.74; 46.10; 45.24; 34.38; 31.31; 28.30 (Boc); 22.29; 18.85; 16.41; 14.00; 11.90. Mass Spectrum (ISMS) m/z 552 ($M+H^+$), calculated for $C_{28}H_{45}N_3O_8$: 551.

The alcohol **A1** was reacted with the Mitsunobu reagents as described by Ma *et al.*, 1995 (Scheme 4.37) as follows: The alcohol **A1** (150 mg, early eluting fraction) was dissolved in dry THF and triphenylphosphine (71 mg) added. To the stirred solution at room temperature under nitrogen was added DEAD (43 uL), and stirring continued for 24 h. Analysis of the crude reaction revealed the formation of a dehydration product ($M+H^+$=534 Da) in moderate yield. Another equivalent of triphenylphosphine/DEAD was added and stirring continued for a further 48 h. The solvent was removed *in vacuo* and the residual oil dissolved in ether/petroleum ether and left to stand to encourage the precipitation of the triphenylphosphine oxide and diethoxycarbonyl hydrazine (white solid, filtered off). The oil remaining after evaporation of the filtrate was purified by flash chromatography eluting with petroleum ether and 10-100% ether in petroleum ether, yield was ~40% (60 mg). TLC ethyl ether Rf=0.61. The NMR spectra were quite complex, as may be expected from the possible mixture of diastereomers/ rotamers. However, it was possible to clearly identify the alanine spin system with H□ at 4.71 ppm (1H, broad pentuplet, J~8Hz). 1D decoupling experiments were performed: irradiation at 4.7 ppm caused the collapse of two signals to singlets, a doublet centred on 1.40 ppm (J=7Hz, alanine H□), and a broad doublet (1H, J=8Hz) at 5.62ppm (alanine NH). These assignments were confirmed by irradiation at 1.4 ppm which caused collapse of the multiplet at 4.71 ppm to a doublet with J=8Hz. The presence of the NH proton in the alanine spin system rules out the □-turn

mimetic **A2** proposed by Ma *et al.*, 1995 as a possible structure for the product, and leaves open the possibility of **A6** or **A7** (Scheme A3) which we felt were more probable products, as the true structure. **^{1}H NMR** (300 MHz, $CDCl_3$): (selected peaks) □ 5.62, ~1H, bd, J=8 Hz; 4.71, ~1H, m(q); 1.40, d, J=6.8 Hz. Decoupling experiments: irradiate 1.4 ppm -> 4.71 = doublet, J=8 Hz; irradiate 4.71 ppm -> 1.4 = singlet, 5.62 = singlet. **^{13}C NMR** (75 MHz, $CDCl_3$): the spectra were difficult to analyse due to the presence of rotamers/diastereomers, peak broadening and impurities which co-eluted. There were a couple of notable features: (i) the appearance of a new peak at the relatively unusual shift of 160.7 ppm possibly due to the carbamate derived oxazoline carbon (only one carbamate resonance was observed, 155.5 ppm), and (ii) the downfield shift of the tertiary Boc carbon resonance which was observed at 81.22 ppm, whereas NHBoc tertiary carbon shifts are normally at a shift upfield of 80 ppm (e.g. 78.9 in the alcohol precursor). Mass Spectrum (ISMS) m/z 534 (MH^+), calculated for $C_{28}H_{43}N_3O_7$: 533.

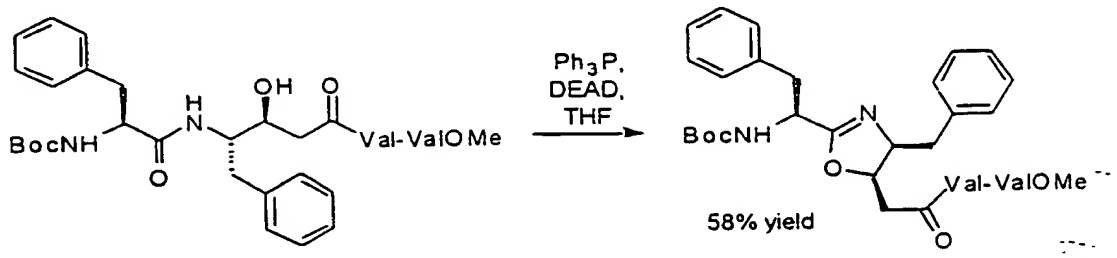
To confirm the results of the NMR analysis a further experiment was carried out. The product material was hydrogenated (EtOH, Pd-C) to remove the Z group. If the product has structure **A6** or **A7** then the amine will now be free to form the diketopiperazine **A8**, a facile reaction in such a system, Scheme A3. If any of the target □-turn mimetic **A2** is present then it will be deprotected to the (very stable) free amine **A9** and be easily detected in the ionspray mass spectrum (ISMS). Analysis of the product mixture from the hydrogenation revealed the presence of a mass peak corresponding to the diketopiperazine (MH^+=354Da), but <u>no trace whatsoever</u> of **A9** (MH^+=400Da).



Scheme A3

Finally, it was also observed that the cyclisation product (which we propose to be **A6**) was easily hydrolysed by dilute aqueous acid (e.g. room temperature 0.1% aq. TFA, 12 h), back to the alcohol **A1** (or a compound of the same mass). This last observation is more consistent with the product structure being the oxazoline **A6** rather than the aziridine **A7** as the oxazoline is more probably subject to facile hydrolysis by aqueous acid, the facile hydrolysis is entirely inconsistent with the structure **A2** proposed by Ma *et al.*, 1995

In further support of **A6** as the product structure, peptide alcohols similar in structure to **A1** have been reported to form oxazolines, (Galéotti *et al.*, 1992) for example:



Other evidence against formation of **A2** by the Mitsunobu reaction as proposed by Ma *et al.*, 1995 is presented below.

(1) Difficulty of forming seven membered rings via the Mitsunobu reaction

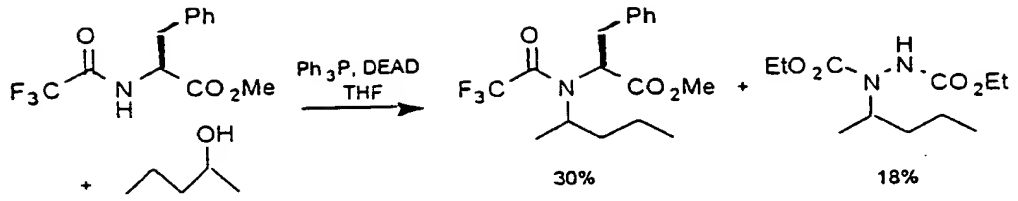
(a) Literature precedent

The literature on the formation of cyclic amines and amides with the Mitsunobu reaction contains numerous examples of the formation of 3-6 membered rings (Carlock and Mack, 1978; Robinson *et al.*.1983; Pfister, 1984; Kelly *et al.*, 1986; Henry *et al.*, 1989; Bernotas and Cube, 1991), but very few cases of seven membered ring formation. In one paper on the cyclisation of amino alcohols the faliure to form a simple seven membered target is specifically described (Bernotas and Cube, 1991) In the organic reactions entry on the Mitsunobu reaction (Hughes, 1992) three instances of seven membered ring formation with carbon-nitrogen bond formation are described: all three involve a primary alcohol, two occur in polycyclic systems and appear to be special cases, and the third involves alkylation of a hydroxamide - far easier than an amide due to higher NH acidity.

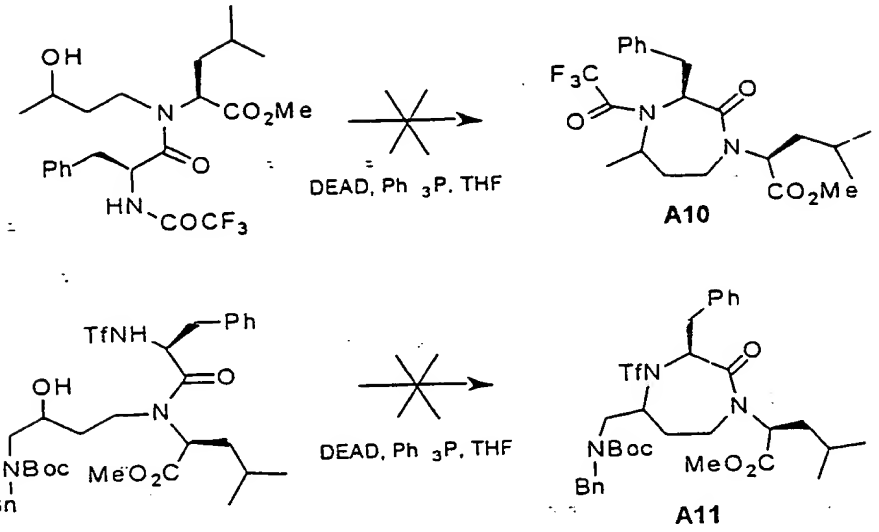
There appears to be no literature precedent for the formation of a seven membered ring to a simple amide or carbamate nitrogen. In addition there is little precedent for secondary amide N-alkylation with hindered secondary alcohols, as is proposed to occur in the formation of **A2**.

(b) Synthetic studies

Extensive studies on the use of the Mitsunobu reaction for the formation of the target system were carried out in our laboratories prior to becoming aware of the proposed synthesis. In our hands this approach was ineffective. The key reactions are described in Schemes A4 and A5.



Scheme A4

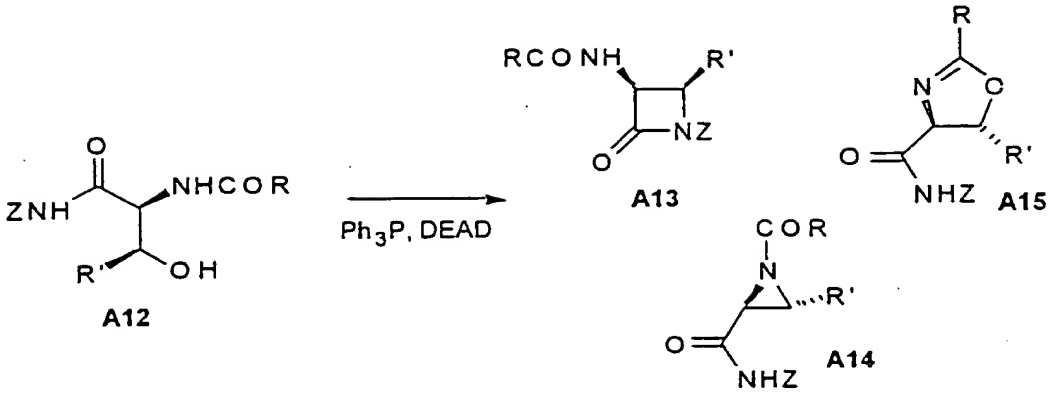


Scheme A5

The formation of the alkylation product was somewhat successful in the intermolecular reaction (Scheme A4), but this success was not repeated in cyclic systems (Scheme A5). No significant amount of the target cyclic products **A10** or **A11** was detected.

(2) Competing reactions - oxazoline and aziridine formation

Cyclisation of □-hydroxy amide derivatives A12 with the aim of forming □-lactams **A13** also results in the formation of the aziridine **A14** and oxazoline **A15** products shown in Scheme A6 (Hughes, 1992). Another example of oxazoline formation was described above (Galéotti *et al.*, 1992).



Scheme A6

As the Mitsunobu reaction is relatively effective for the formation of small ring sizes, it is quite probable that the formation of aziridines and oxazolines will compete with other possible cyclisations, other factors being equal. Such competition can take place in the proposed synthesis, the products would then be **A6** and/or **A7**, Scheme A3. Both the aziridine and oxazoline are isomeric with the target compound **A2**, possibly leading to their confusion with the target, a situation easily resolved by ^{1}H NMR as we demonstrated above.

In summary, the proposed method is in error because:

- We have repeated the cyclisation and found the product to be a structural isomer of the target, probably the oxazoline **A6**.

This finding is supported by:-

- Literature contrindications (competing cyclisations favoured), lack of precedent (seven membered rings difficult to form by the Mitsunobu reaction).
- Extensive studies in our laboratories which indicate the Mitsunobu approach is generally ineffective for the synthesis of the □-turn mimetics.

REFERENCES

Abdel-Magid *et al.*, 1996, Journal of Organic Chemistry **61** 3849-3862

Alkorta *et al.*, 1996, J. Mol. Model. **1** 16-25.

Arrhenius *et al.*, 1987, The chemical synthesis of structured peptides using covalent hydrogen-bond mimics. In Protein Structure, Folding and Design 2 Ed. D. Oxender. Alan R. Liss, Inc. 453-465.

Ball, J.B. and Alewood, P.F., 1990, Journal of Molecular Recognition **3(2)** 55-64.

Ball *et al.*, 1993, Tetrahedron **49(17)** 3467-3478.

Basile *et al.*, 1994, Journal of Organic Chemistry **59** 7766-7773.

Bernotas, R.C. and Cube, R.V., 1991, Tetrahedron Letters **32(2)** 161-164.

Bocoum *et al.*, 1991, Tetrahedron Letters **32** 1367-1370.

Bodansky, M. and Bodansky, A., 1984, The Practice of Peptide Synthesis. Berlin-Heidelberg, Springer-Verlag.

Borch *et al.*, 1971, J. Am. Chem. Soc. **93** 2897-2904.

Boutin, R.H. and Rapoport, H., 1986, Journal of Organic Chemistry **51** 5320-5327.

Brown, H.C., 1975, Organic Syntheses Via Boranes. New York, Wiley.

Brown *et al.*, 1986, Tetrahedron **42** 5515.

Brown, H.C. and Bhat, K.S., 1986, J. Am. Chem. Soc. **108** 293.

Brown, H.C. and Jadhav, P.K., 1983, J. Am. Chem. Soc. **105** 2092-2093.

Brown, H.C. and Jadhav, P.K., 1984, Journal of Organic Chemistry **49** 4089.

Brown, H.C. and Krishnamurthy, 1979, Tetrahedron **35** 567-607.

Brown *et al.*, 1980, Synthesis : 151.

Brown *et al.*,1990, J. Am. Chem. Soc. **112** 2389.

Callahan *et al.*, 1992, JMedChem **35** 3970-3972.

Carlock, J.T.and Mack, M.P., 1978, Tetrahedron Letters **52** 5153-5156.

Carpino *et al.*, 1994, Tetrahedron Letters **35** 2279-2280.

Carpino *et al.*, 1990, J. Am. Chem. Soc. **112** 9651-9652.

Chalmers, D.K. and Marshall, G.R., 1995, J. Am. Chem. Soc. **117**(22) 5927-37.

Chen *et al.*, 1992, PNAS **89**(Biochemistry) 5872-5876.

Cupps *et al.*, 1985, Journal of Organic Chemistry **50** 3972-3979.

Ehrlich *et al.*,1993, Tetrahedron Letters **34** 4781-4784.

Farmer, P.S. and Ariëns, E.J., 1982, Topics in Peptide Science 362-365.

Fehrentz, J.-A. and Castro, B.,1983, SYNTHESIS 676-678.

Frigerio, M. and Sangostino, M., 1994, Tetrahedron Letters **35** 8019-8022.

Früchtel, J.S. and Jung, G., 1996, Angew. Chem. Int. Ed. Engl. **35** 17-42.

Galéotti *et al.*, 1992, Tetrahedron Letters **33**(20) 2807-2810.

Gallop *et al.*,1994, Journal of Medicinal Chemistry **37**1233-1251.

Gardner *et al.*, 1993, Tetrahedron **49**(17) 3433-3448.

Giannis, A. and Kolter, T., 1993, Angew. Chem.,Int. Ed. Engl. **32** 1244-1267.

Gordon *et al.*, 1994, Journal of Medicinal Chemistry **37** 1385-1401.

Greene, T.W. and Wuts, P.G., 1991, Protective Groups. New York, John Wiley & Sons.

Gribble and Nutatits,1985, Org. Prep. Proc. Int. **17** 317.

Griffith, W.P. and Ley, S.V., 1990, Aldrichimica Acta **23** 13-19.

Guilbourdenche *et al.*, 1994, Bull. Soc. Chim. Belg. **103**(1) 1-8.

Henry *et al.*, 1989, Tetrahedron Letters **30**(42) 5709-5712.

Hirschmann *et al.*, 1993, J. Am. Chem. Soc. **115** 12550-12568.

Hirschmann *et al.*, 1992, J. Am. Chem. Soc. **114** 9217-9218.

Hirschmann *et al.*, 1996, Tetrahedron Letters **37** 5637-5640.

Hölzemann, G., 1991, Kontakte (Darmstadt) 3-12.

Hölzemann, G.,1991, Kontakte (Darmstadt) 55-63.

Hudlicky, M., 1990, Oxidations in Organic Chemistry. Washington, American Chemical Society.

Huffman *et al.*, 1989, Mimics of Secondary Structural Elements of Peptides and Proteins. Synthetic Ppetides: Approaches to Biological Problems . Alan R. Liss, Inc. 257-266.

Huffman *et al.*, 1988, Reverse turn mimics. Peptides: Chemistry and Biology, Proceedings of the Tenth American Peptide Symposium Ed. G. R. Marshall. Leiden, The Netherlands, ESCOM. 105-108.

Hughes, D.L., 1992, Organic reactions **42** 335-656.

Humphries *et al.*, 1994, Exp. Opin. Ther. Patents **4**(3) 227-235.

Hutchins, R.O. and Natale, N.R., 1979, Org. Prep. Proc. Int. **11** 203-241.

Jurczak, J. and Golebiowski, A., 1989, Chem. Rev. **89** 149-164.

Kahn, M., 1993, SYNLETT 821-826.

Kahn, M., 1996, Library of conformationally constrained reverse- turn peptides. 64 pp. PCT Int. Appl., Molecumetics, Ltd., USA.

Kelly *et al.*, 1986, Journal of Organic Chemistry **51** 95-97.

Kessler *et al.*, 1995, Letters in Peptide Science **2** 155-160.

Knapp *et al.*, 1992, Journal of Organic Chemistry **57** 6239-6256.

Koskinen, A.M.P. and Rapoport, H., 1989, Journal of Organic Chemistry **54** 1859-1866.

Kramer, G.W. and Brown, H.C., 1974, Journal of Organometallic Chemistry **73** 1-15.

Kramer, G.W. and Brown, H.C., 1977, Journal of Organometallic Chemistry **132** 9-27.

Krstenansky *et al.*, 1982, Biochem. Biophys. Res. Commun. **109** 1368-1374.

Kuntz, I.D., 1972, J. Am. Chem. Soc. **94** 4009-4012.

Lewis *et al.*, 1973, Biochim. Biophys. Acta **303** 211-229.

Ma, X. *et al.*, 1995, Protein and Peptide Letters 347-350.

Meier, H. and Zeller, K., 1975, Angew. Chem.,Int. Ed. Engl. **14** 32-43.

Milner-White, E.J.,1988, Journal of Molecular Biology **204** 777-782.

Nahm, S. and Weinreb, S.M., 1981, Tetrahedron Letters **22(39)** 3815-3818.

Nakanishi, H. and Kahn, M., 1996, Design of Peptidomimetics. The Practice of Medicinal Chemistry . Academic Press Limited. Ch. 27, 571-590.

Newlander *et al.*, 1993, JMedChem **36** 2321-2331.

Olson *et al.*, 1993, Journal of Medicinal Chemistry **36** 3039-3049.

Pelter *et al.*, 1988, Borane Reagents. New York, Academic Press.

Pfister, J.R., 1984, Synthesis 969-970.

Qabar *et al.*, 1996, Letters in Peptide Science **3** 25-30.

Racherla *et al.*, 1992, Journal of Organic Chemistry **57** 6614-6617.

Ray, R. and Matteson, D.S., 1980, Tetrahedron Letters **21** 449-450.

Richardson, J.S., 1981, Adv. Prot. Chem. **34** 167-339.

Robinson *et al.*, 1983, Journal of Organic Chemistry **48** 5396-5398.

Rose *et al.*, 1985, Advan. Protein Chem. **37** 1-109.

Sardina, F.J. and Rapoport, H., 1996, Chem. Rev. **96** 1825-1872.

Soderquist, J.A. and Najafi, M.R., 1986, Journal of Organic Chemistry **51** 1330.

Szeja, W., 1985, Synthesis 983.

Thompson, L.A. and Ellman, J.A., 1996, Chem. Rev. **96** 555-600.

Valle *et al.*, 1989, International Journal of Peptide and Protein Research **33** 181-190.

VanRheenen *et al.*, 1976, Tetrahedron Letters **23** 1973-1976.

Virgilio, A.A. and Ellman, J.A., 1994, J. Am. Chem. Soc. **116(25)** 11580-1.

Virgilio *et al.*, 1996, Tett. Lett. **37** 6961-6964.

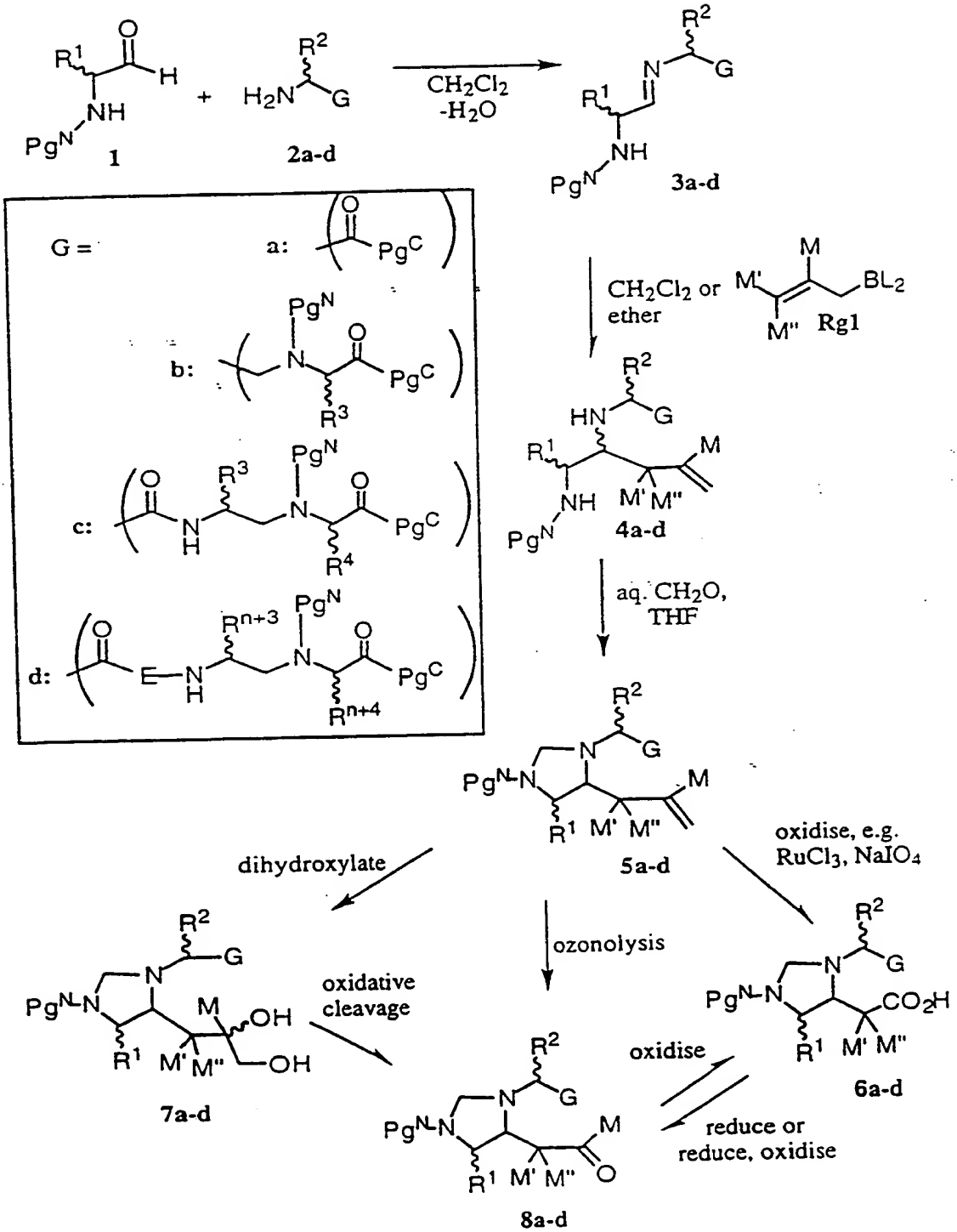
Wenschuh *et al.*, 1994, Journal of Organic Chemistry **59**: 3275-3280.

Wilmont, C.M. and Thornton, J.M., 1990, Protein Engineering **3** 479-493.

Wolf, J. and Rapoport, H., 1989, Journal of Organic Chemistry **54** 3164-3173.

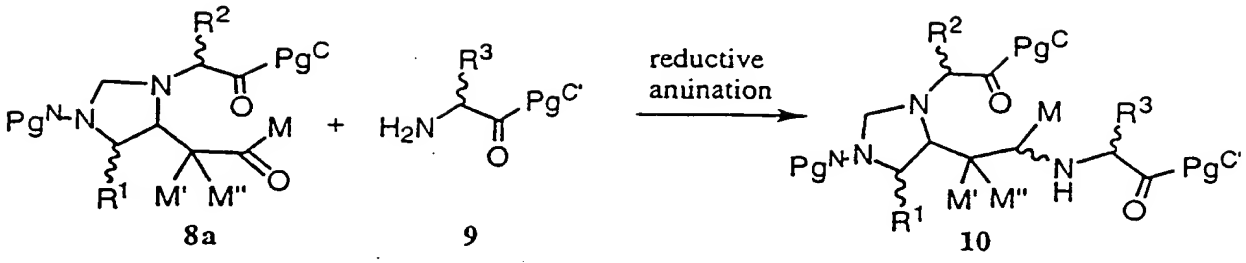
Yamamoto, Y. and Asao, N., 1993, Chem. Rev. **93** 2207-2293.

SCHEME 1

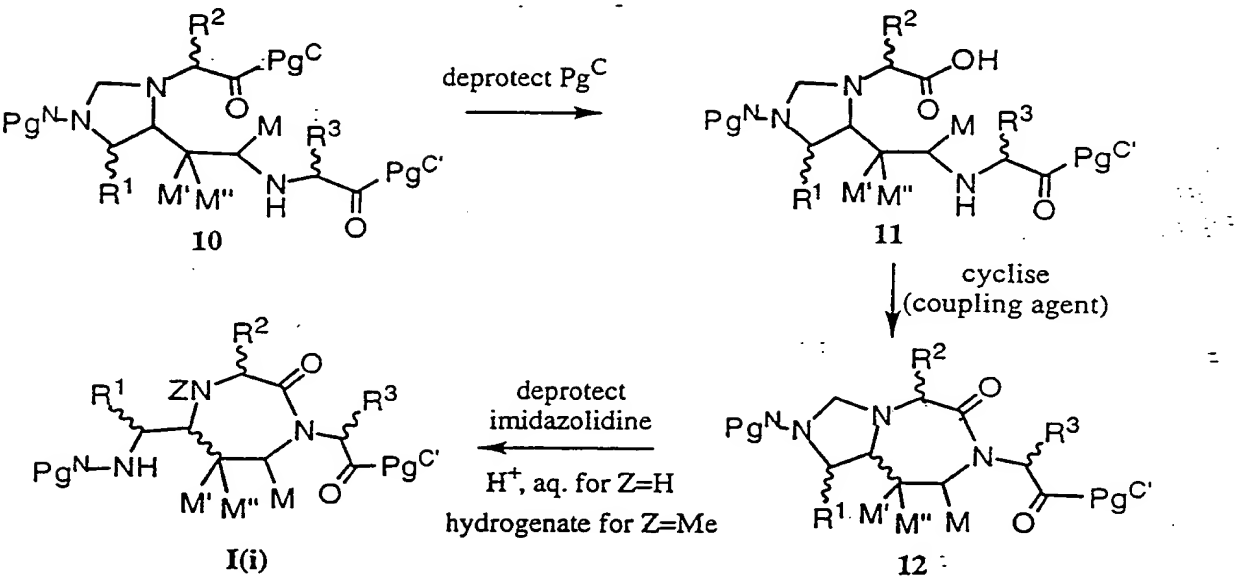


Scheme 1

SCHEMES 2 AND 3

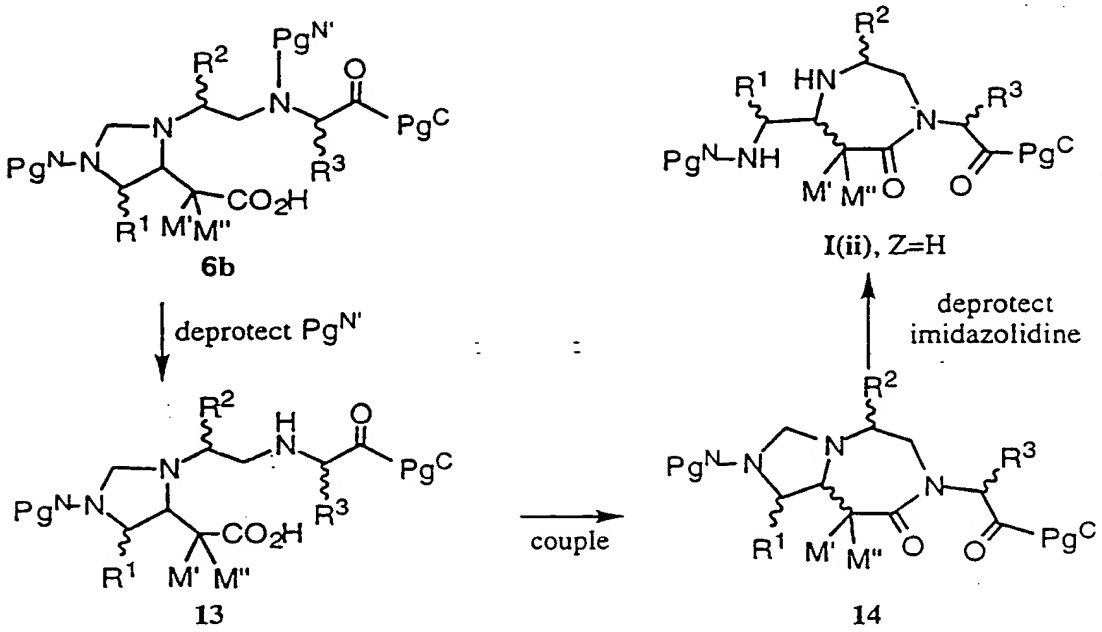


Scheme 2



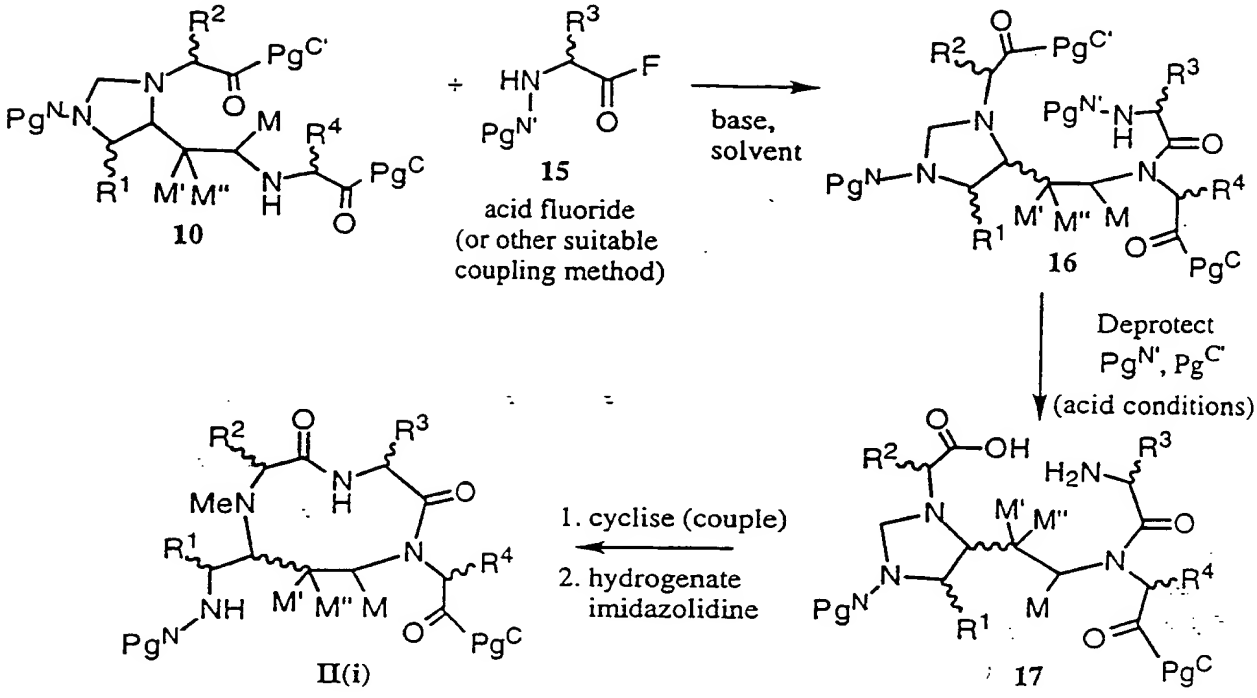
Scheme 3. Synthesis of γ-turn mimetics I(i).

SCHEME 4

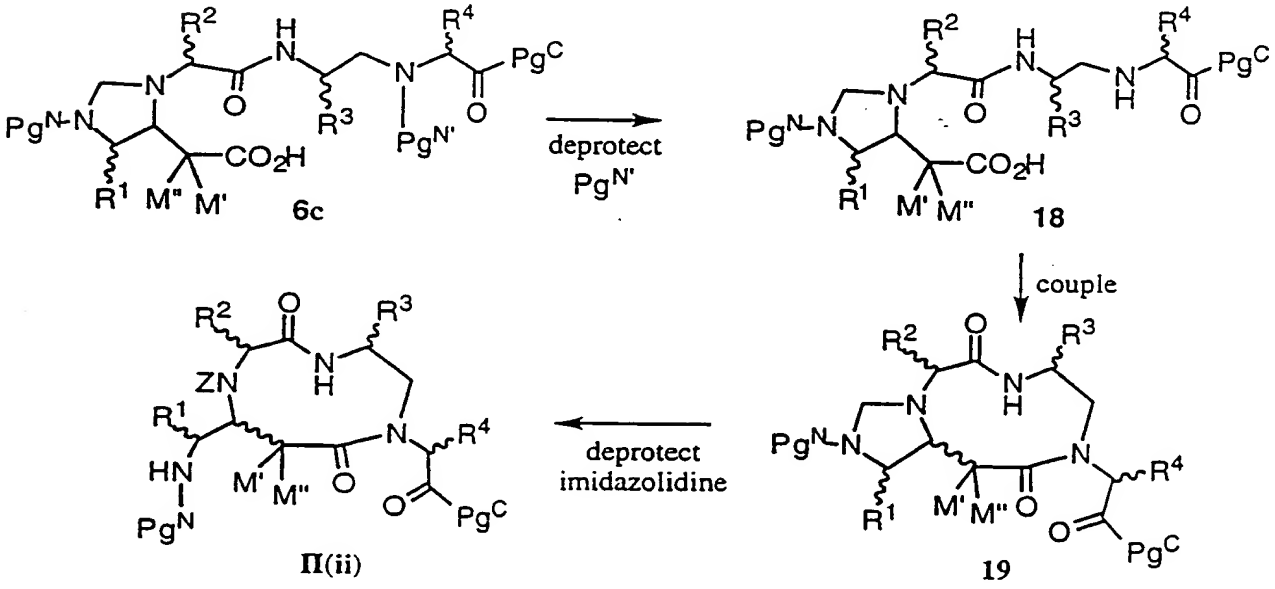


Scheme 4. Synthesis of γ-turn mimetics **I(ii)**.

SCHEMES 5 AND 6

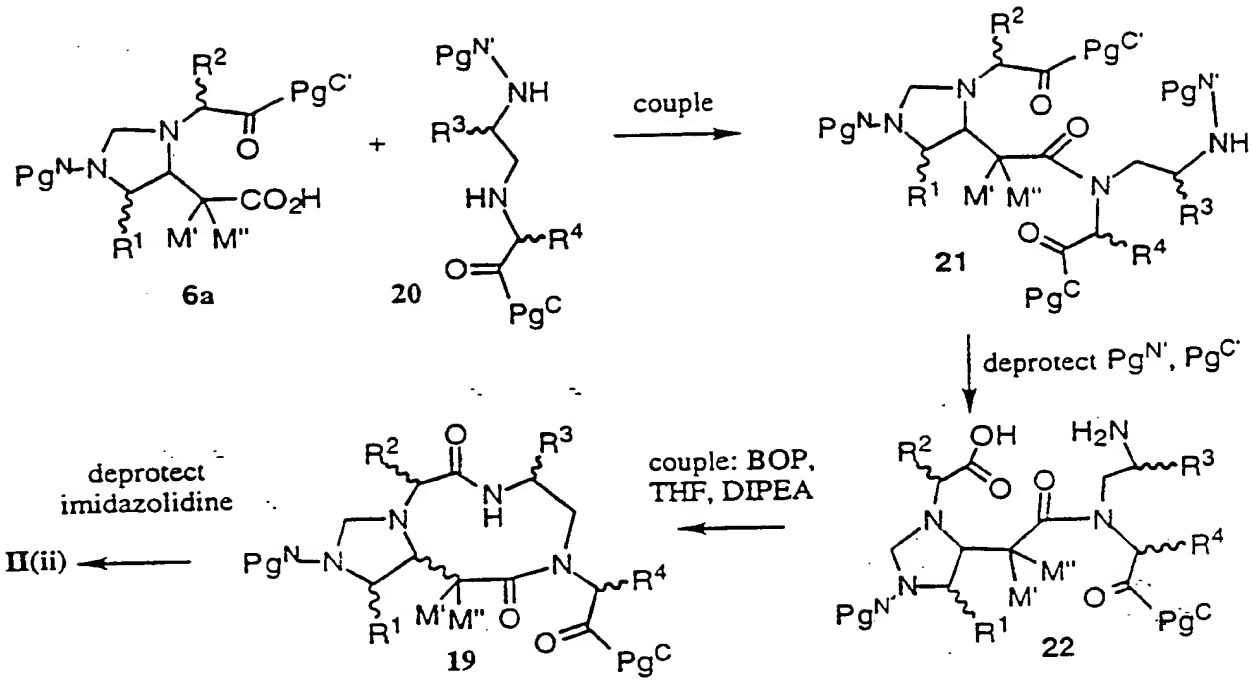


Scheme 5. Synthesis of of β-turn mimetics II(i).

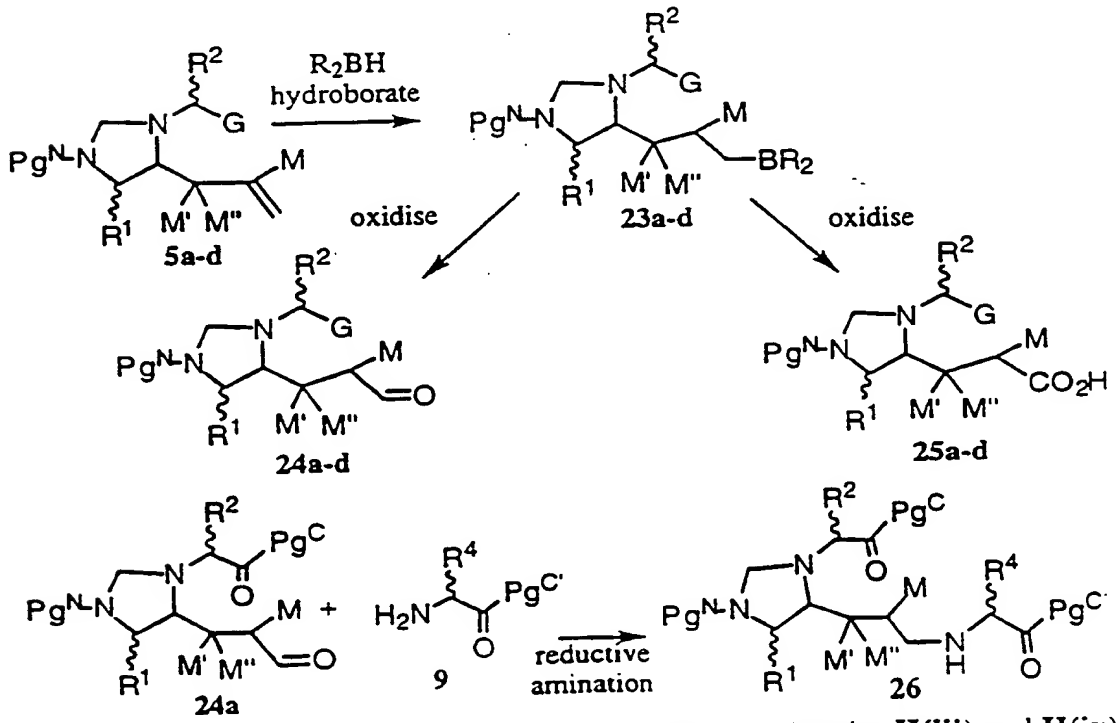


Scheme 6. Synthesis of β-turn mimetics II(ii).

SCHEMES 7 AND 8

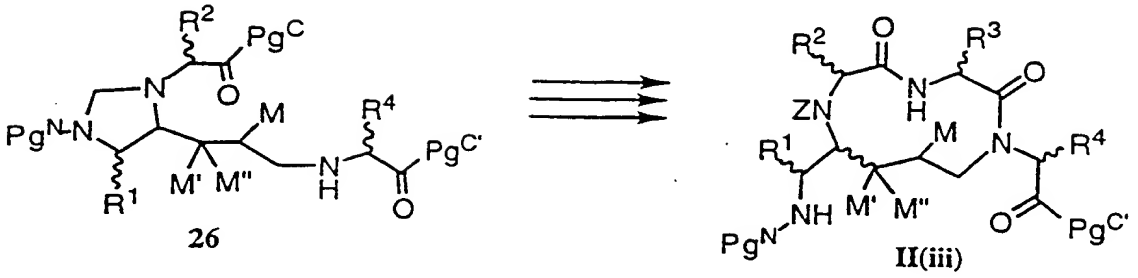


Scheme 7. Alternative synthesis of beta turn mimetics II(ii)

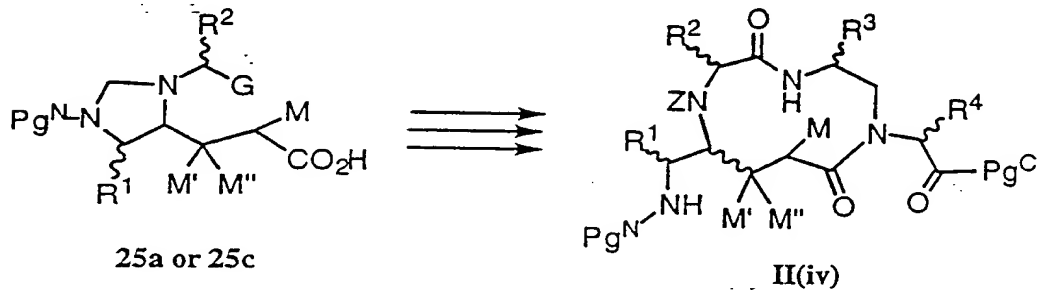


Scheme 8. General methods used in the synthesis of mimetics II(iii) and II(iv)

SCHEMES 9 AND 10

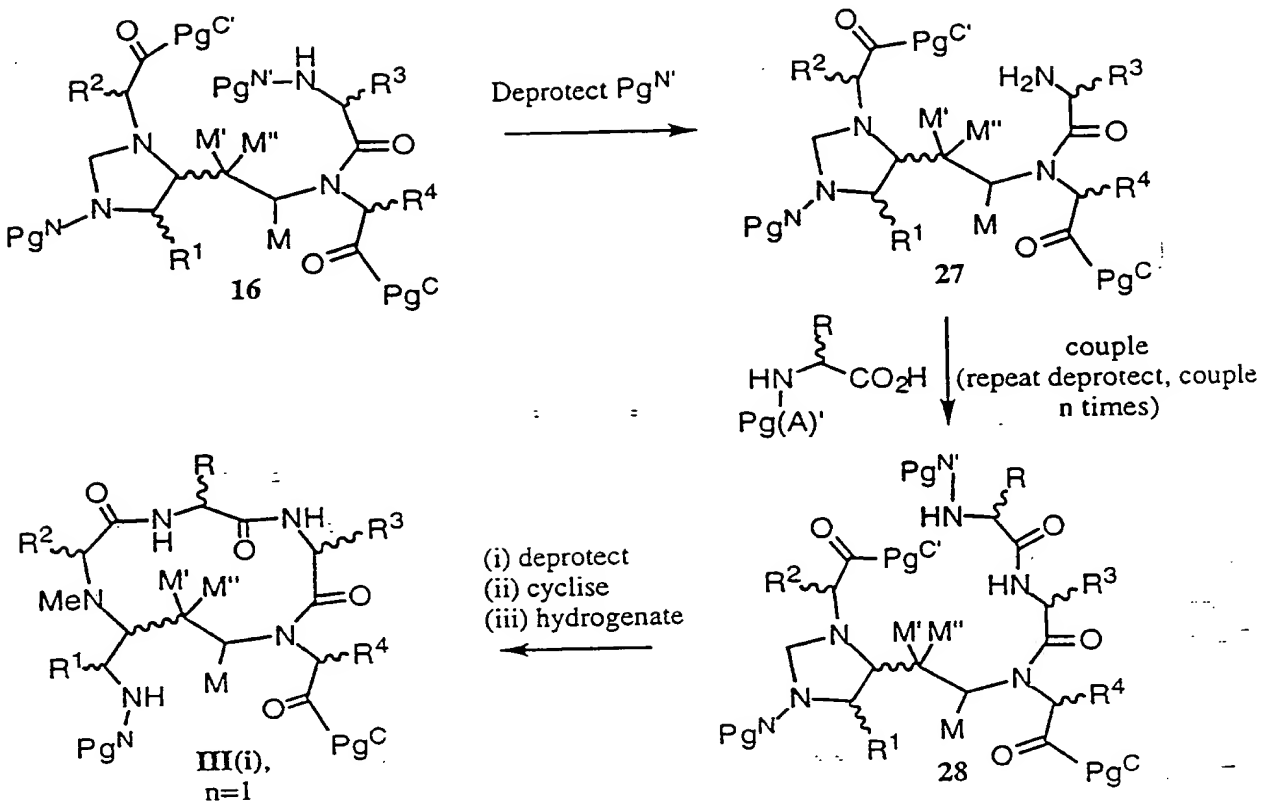


Scheme 9. Synthesis of beta turn mimetics **II(iii)**: Same method as described in Scheme 5, substituting **26** for **10**.



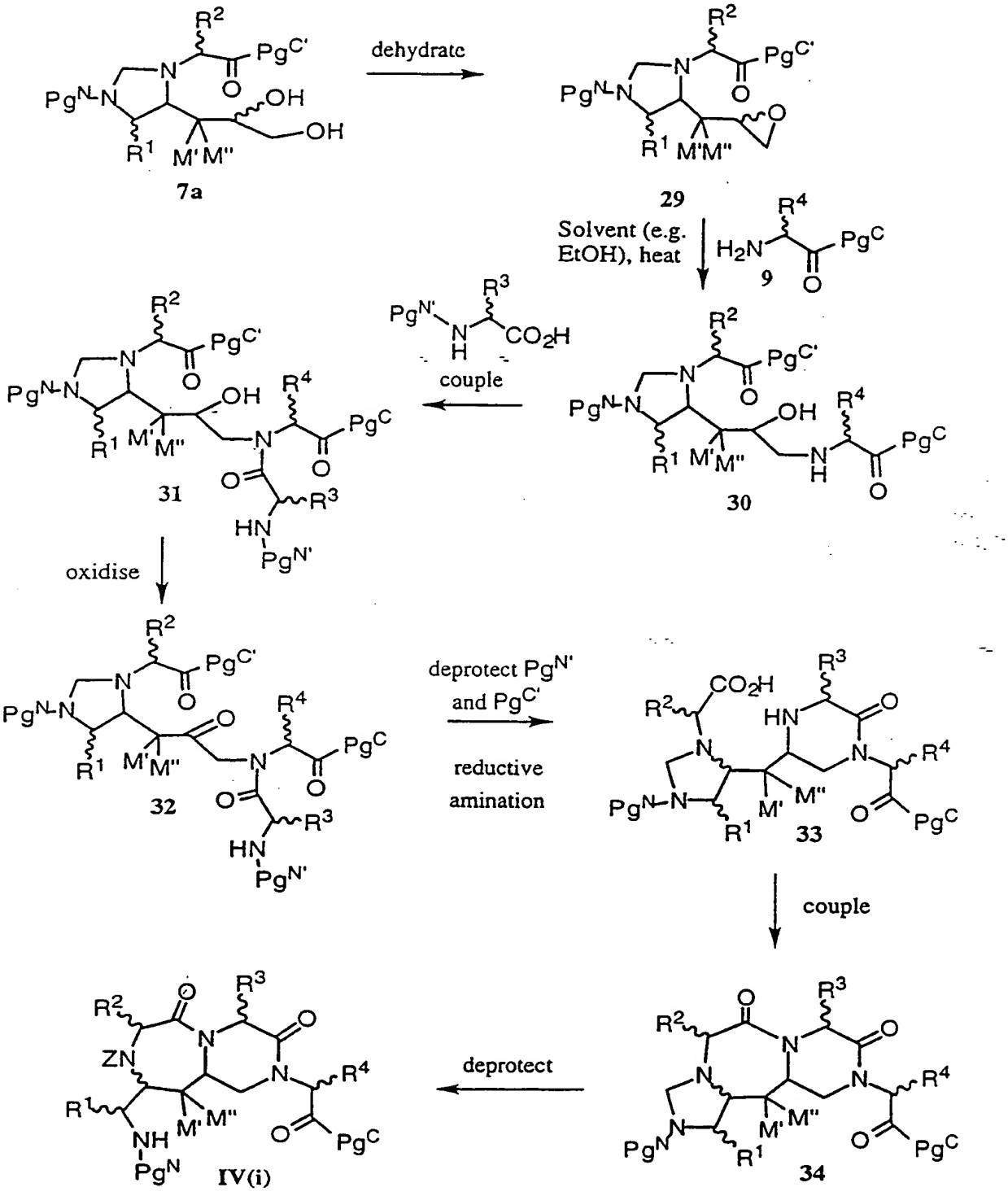
Scheme 10. Synthesis of beta turn mimetics **II(iv)**: same method as described in Scheme 6, substituting **25c** for **6c**; alternatively, same method as for Scheme 7, substituting **25a** for **6a**.

SCHEME 11



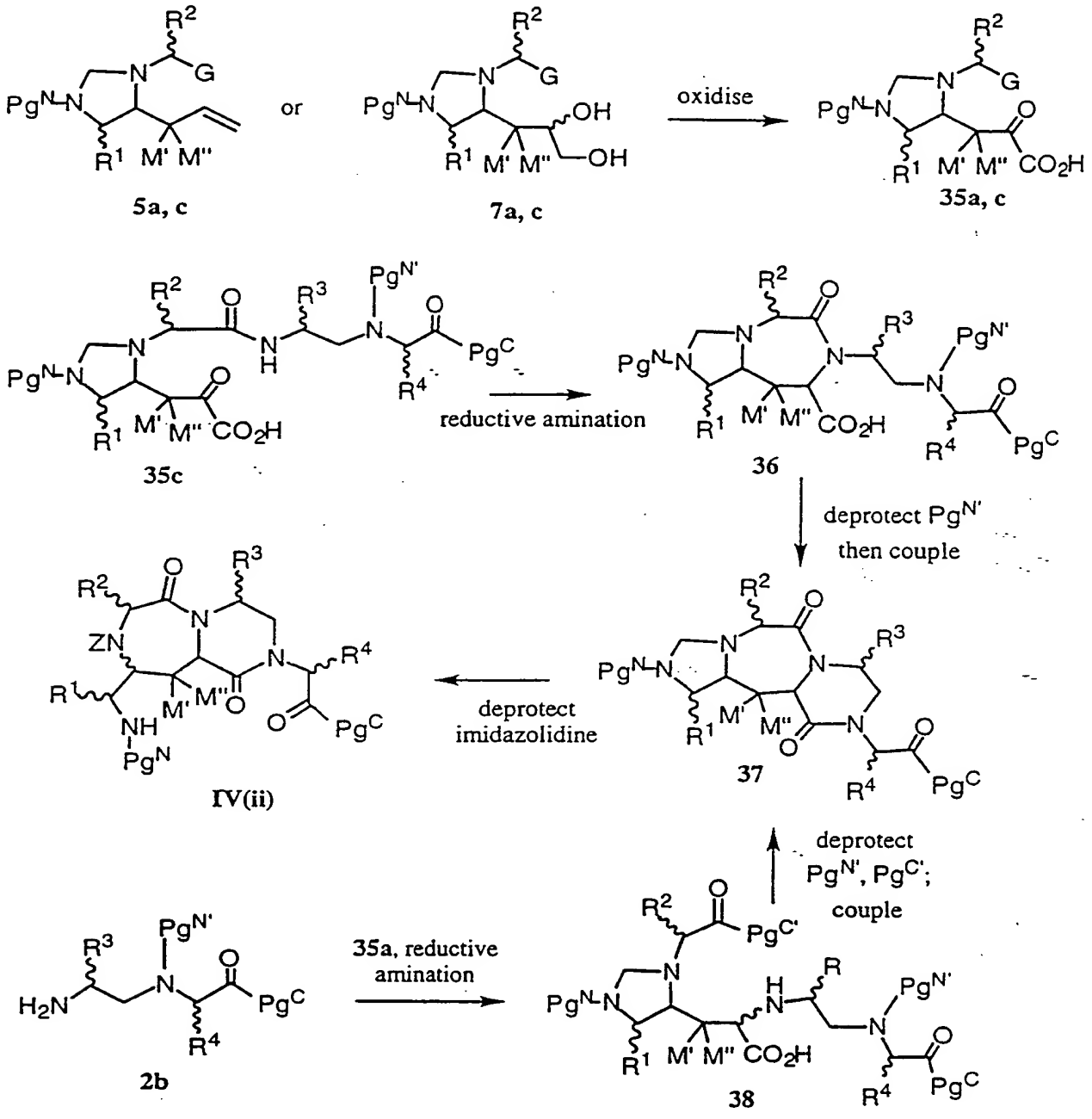
Scheme 11. Synthesis of beta buldge mimic III(i) using the general method for the synthesis of II(i) (as described in Scheme 5).

SCHEME 12



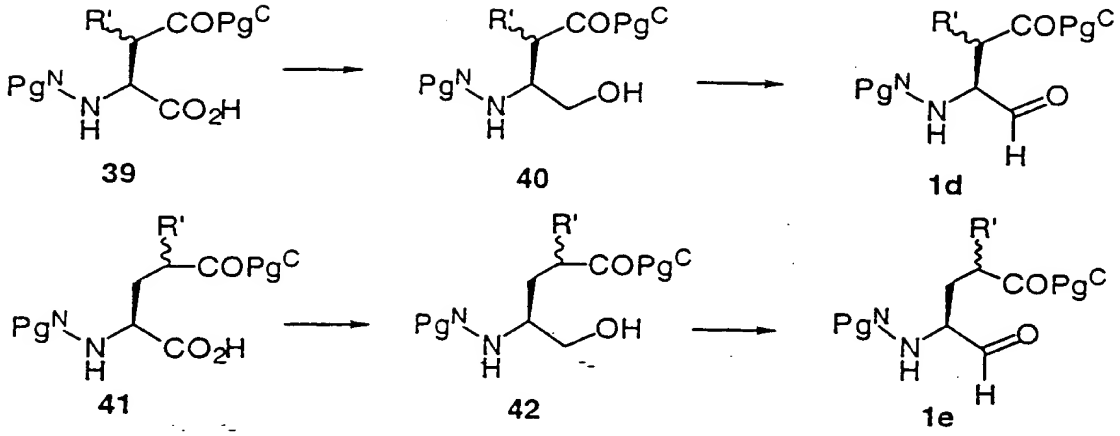
Scheme 12. Synthesis of bicyclic β-turn mimetic systems **IV(i)**.

SCHEME 13

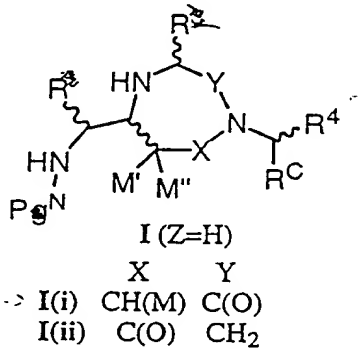


Scheme 13. Synthesis of bicyclic beta turn mimetic systems IV(ii).

SCHEMES 14 AND 15

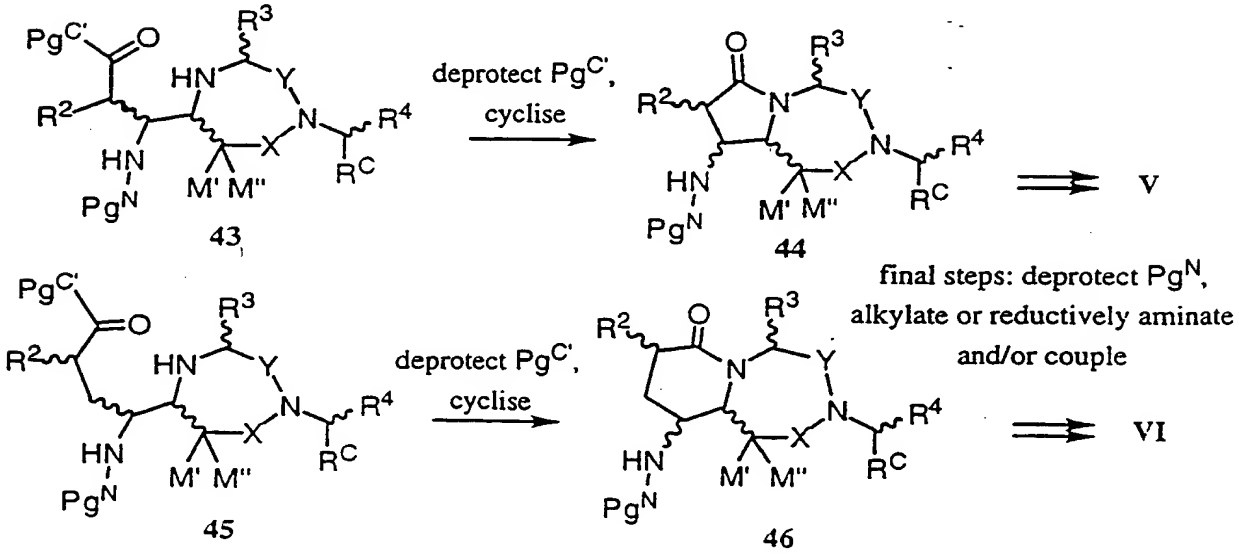


Scheme 14. Alkylated aspartic and glutamic acid derivatives. See text for methods.



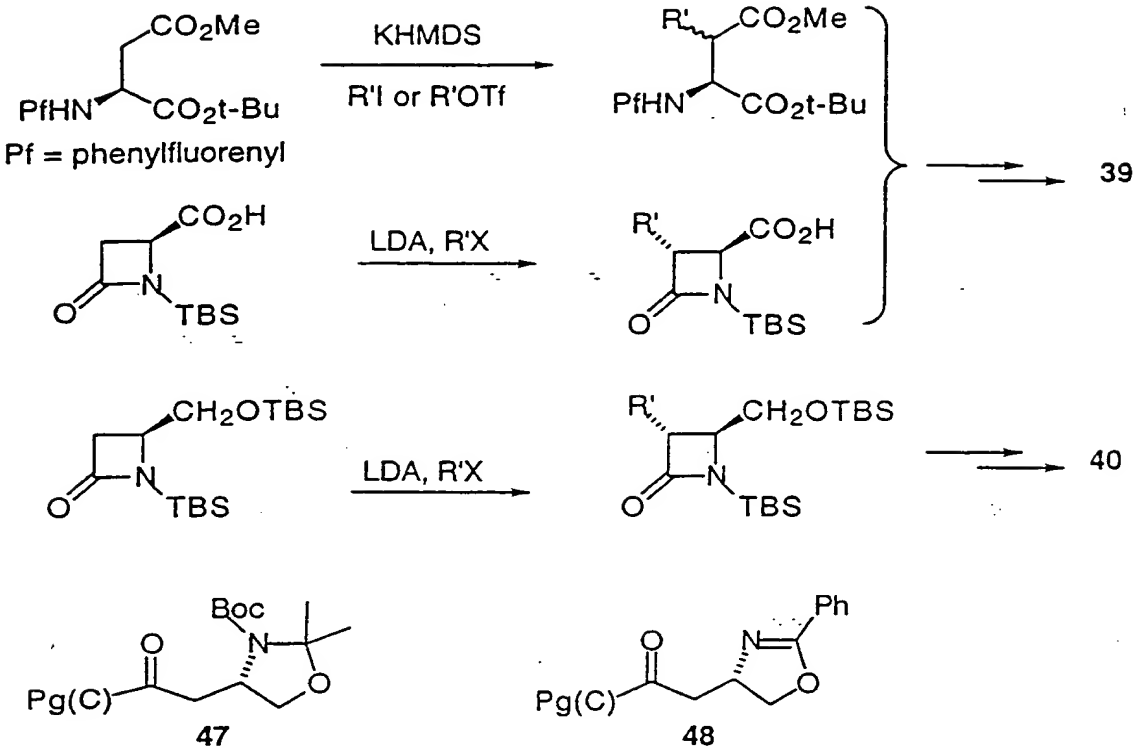
I (Z=H)

	X	Y
I(i)	CH(M)	C(O)
I(ii)	C(O)	CH_2



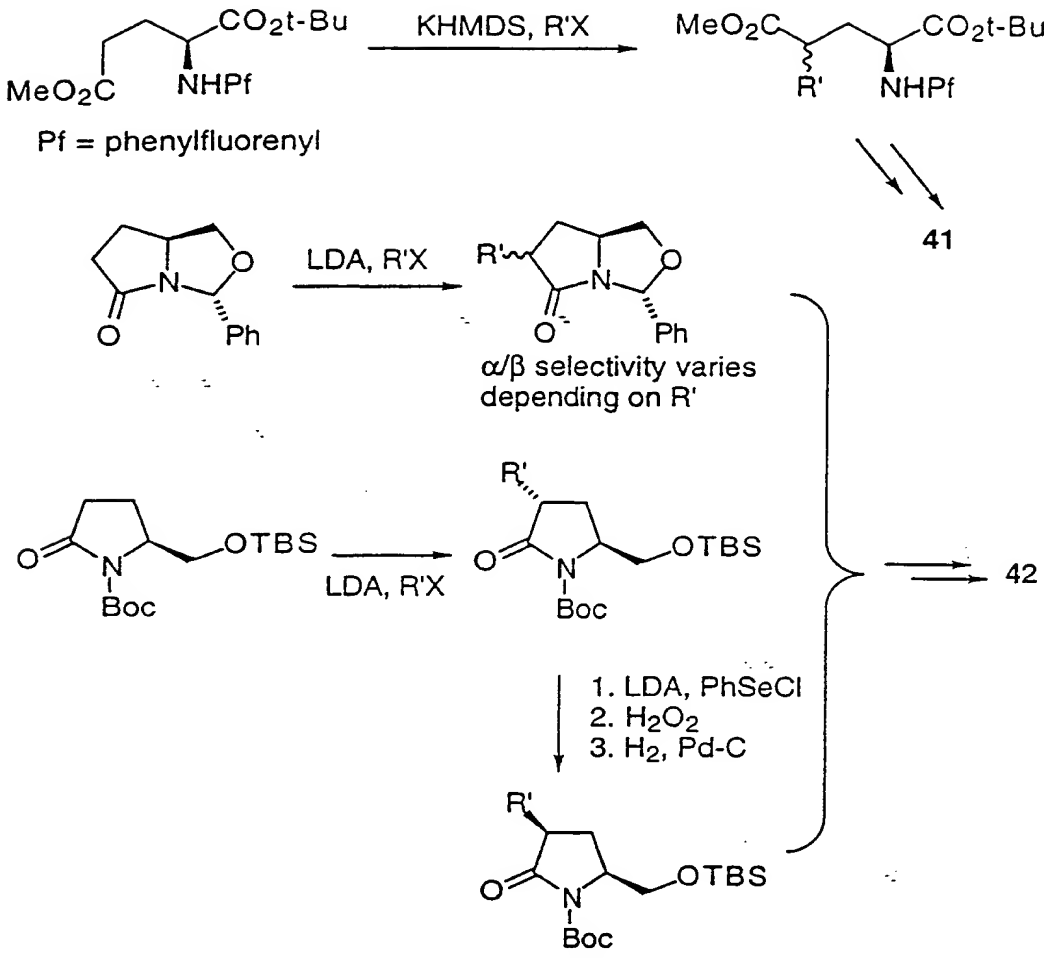
Scheme 15. Synthetic methods for the neutral bicyclic β-turn mimetics V and VI.

SCHEME 16



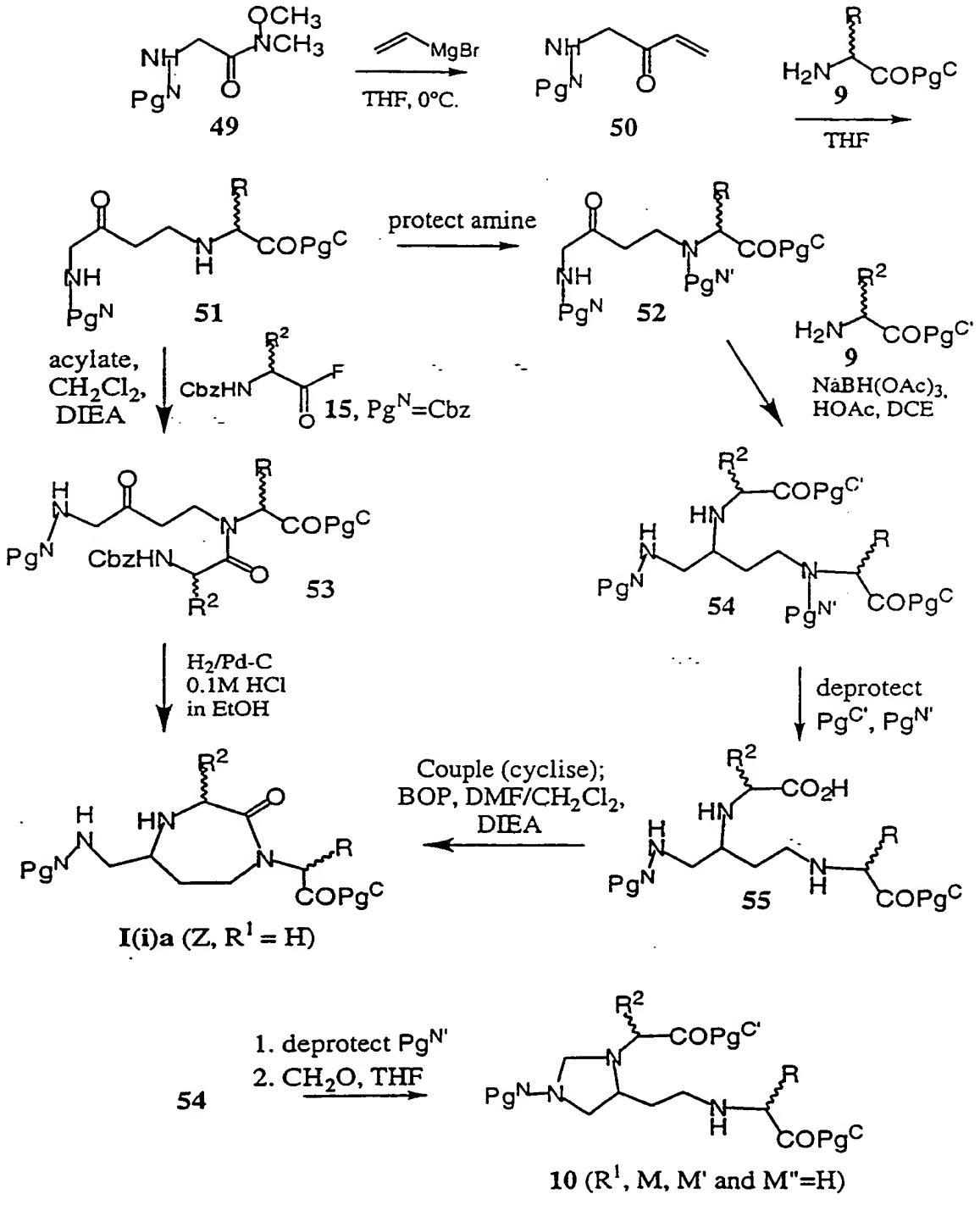
Scheme 16. Alkylation of aspartic acid derivatives.

SCHEME 17



Scheme 17. Alkylation of glutamic acid derivatives.

SCHEME 18



Scheme 18. Shorter procedure for the preparation of **10** and **I(i)a** where R^1 is hydrogen.